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Mini review

Medical diseases affecting lower urinary tract function☆

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ABSTRACT

To date, some functions of the lower urinary tract are not fully understood. Lower urinary tract disorders such as lower urinary tract symptoms and overactive bladder are debilitating conditions with a negative impact on quality of life. The major medical diseases, which have systemic effects on their victims, may play a role in the disturbance of the lower urinary tract function. Recent studies provide further evidence that a number of medical diseases such as chronic heart failure, chronic obstructive pulmonary disease, constipation, chronic kidney disease, autoimmune diseases, and metabolic syndrome can affect the lower urinary tract function via the disease mechanisms. Our aim was to summarize and analyze the results of epidemiological surveys and recent advances in the understanding of systemic disease-related lower urinary tract dysfunction. We expect our findings to indicate some areas for future research in this topic.

1. Introduction

Micturition is a complicated process in which the coordination of bladder relaxation in the filling phase and bladder contraction and sphincter relaxation during the voiding phase is essential.[1] These processes are regulated by vesical afferent and efferent pathways and a neuropepetide control system, and the detrusor contains multiple receptors and signaling pathways. Disturbances in micturition function may result in lower urinary tract symptoms (LUTS). LUTS is a group of urinary symptoms related to the storage, emptying, and postmicturition phases.[2] Aggravation of LUTS has a profound impact on the patient's quality of life.

LUTS typically develop as a result of primary bladder dysfunction or occur secondary to prostatic obstruction in the urological field. However, many diseases can affect lower urinary tract function by causing mechanical effects, urine overproduction, immune reactions, peripheral nerve damage, pelvic vascular ischemia, and viscero–vesical interactions. In epidemiological studies, the prevalence of LUTS was found to be high in certain demographic groups such as aged people, middle-aged women, and children.[3] The prevalent diseases in these populations may influence lower urinary tract function via various disease mechanisms. In cases involving diseases such as chronic heart failure (CHF), chronic obstructive pulmonary disease (COPD), constipation, chronic kidney disease (CKD), autoimmune diseases, and metabolic syndrome, the long-term and systemic effects of disease progression on lower urinary tract function are overlooked by physicians and scientists. Therefore, we conducted this review to compile the data on this topic and identify the scope for further studies in this field.

2. CHF and LUTS

CHF is a medical condition in which the heart is unable to supply sufficient blood for tissue metabolism. The incidence of heart failure in persons aged more than 65 years can be as high as 10 cases per 1000 population.[4] Because fluid retention and peripheral edema in patients with CHF usually necessitate administration of diuretics, these patients are also likely to experience changes in urinary frequency. Certain risk factors for CHF, including hypertension,[5] diabetes mellitus,[6] and obesity, also cause LUTS in aged adults. Therefore, it would be of particular interest to determine the interaction between CHF and the development of LUTS.

Nocturia, urinary incontinence, and overactive bladder (OAB) are prevalent in patients with CHF. Fatigue, late-stage heart failure, high body mass index, and diuretic use are associated with the development of LUTS, particularly in patients showing symptoms of OAB. When accompanied by hypertension and fluid retention, CHF may affect nocturia by inducing increased nocturnal urine production. Additionally, Mckeique and Reynard[5] suggested that a reversal of the circadian rhythm results in a disorder of sodium excretion in the elderly, which can cause nocturnal polyuria. They also proposed the association between nocturnal polyuria and heart failure. Arteriosclerosis and pelvic ischemia could be common pathogenic factors for both CHF and OAB. Palmer et al[7] reported

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that high degrees of chronic fatigue and depression are associated with OAB in CHF patients because of the resultant dysfunction of the autonomic nervous systems. Late-stage heart failure and constipation also contribute to the presence of OAB symptoms. Chiu et al[8] further indicated that among patients with LUTS, storage symptoms are more severe in patients who also have CHF, particularly in patients with a New York Heart Association Classification equal to or greater than class III. The role of diuretics in the development of OAB in CHF patients is still a matter of debate because fluid overproduction related to diuretic use may not cause urgency, which is the cardinal symptom of OAB. However, Ekundayo et al[9] showed that loop diuretics may increase the prevalence of OAB symptoms in aged adults. Diuretic-induced rapid production of urine may add urgency to diuretic-associated high urinary frequency by triggering DO in the aging bladder.[9]

Patients with CHF experience OAB symptoms that can have a negative impact on quality of life. Although the prevalence of OAB in CHF patients is high (57%), few patients seek medical treatment for their OAB.[7] It should be noted that CHF patients with OAB may have more severe cardiovascular comorbidities, including hypertension, pulmonary heart disease, cerebrovascular disease, renal disease, and diabetes.[10] The antimuscarinics administered to patients showing CHF with OAB may result in an elevated heart rate.[11] An increased heart rate in these patients might reflect an underlying autonomic imbalance, with increased sympathetic and decreased parasympathetic tone, and could increase myocardial oxygen consumption.[11] Because of the negative effects of antimuscarinics on cardiovascular function, physicians should carefully evaluate the use of antimuscarinics for CHF patients with OAB.

3. COPD and LUTS

COPD is a disease that can affect lower urinary tract dysfunction by causing pharmacophysiological changes in bronchioles and increased intra-abdominal pressure during chronic cough. The manifestations of COPD include cough, chronic sputum production, wheeze, and dyspnea.[12] Chronic cough is the best single symptom to predict airway obstruction in smokers older than 60 years[13]; furthermore, chronic cough directly affects pelvic wall weakness and aggravates urinary incontinence. Therapeutic agents for COPD, such as inhaled beta-agonists, anticholinergics, and corticosteroids, may also affect lower urinary tract function.

The international prevalence of COPD is 5% and 16% in patients aged 40 years and older, respectively, and the prevalence depends on the country in which the patient resides.[14] The prevalence and mortality rate of COPD patients have declined because of smoking cessation and improving health care in recent decades.[15] Several large epidemiological studies indicated that different symptoms of LUTS are associated with COPD in males and in females. Hirayama et al[16] reported that 10% of COPD male patients older than 40 years have urinary incontinence. Among patients with urinary incontinence, 63% of men developed urgent incontinence. In another community-based study, Jackson et al[17] showed that 21% of women may experience urinary incontinence at least once per week. Female COPD patients may show up to a 5.6-fold higher risk of stress urinary incontinence.

The mechanisms underlying gender-based differences in LUTS presentations are still unclear, and the management of LUTS in COPD patients is a matter of debate as well. Hirayama et al[18] suggested an inverse association between urinary incontinence and respiratory function in men. Thus, the use of beta-agonists to treat COPD can improve 1st-second forced expiratory volume (FEV_1)% and decrease urinary incontinency in men with COPD. However, cough is the major cause of urinary incontinency among 80–90% of female with cystic fibrosis.[19] Frequent coughing and dyspnea may lead to chronic ischemia and imbalance within the muscles of the abdominopelvic capsule. Cough-related urinary incontinence is common in patients with COPD and is largely overlooked. However, this condition can significantly alter the patient's quality of life. Systematic questioning by the physician would facilitate prompt referral for appropriate therapeutic interventions, such as Kegel exercise.

4. Constipation and LUTS

Constipation is a common medical condition among outpatients. Constipation is defined by less than three bowel movements per week, with stools that are usually hard, dry, small in size, and difficult to eliminate. The prevalence of chronic idiopathic constipation is 14%.[20] Anatomically, the rectum neighbors the bladder, and they differentiate from a common embryological origin in the cloaca.[3] The motor nerve supply to each organ arises from the same outflow, S2–S4; for example, the pudendal nerve innervates both the anal and urethral striated sphincters. Moreover, the pelvic floor weakness caused by the severe straining that arises from constipation may contribute to the development of stress urinary incontinence. In epidemiological studies, researchers reported that children, middle-aged women, and geriatric patients could be simultaneously affected by constipation and LUTS.[20–22]

Functional constipation in the pediatric population is common, with the prevalence ranging from 4% to 37% in different reports.[21] Children with constipation have a higher prevalence of OAB,[22] as well as fecal and urinary incontinence,[21] than children without constipation. Loening-Baucke[21] reported that 22.6% of American children have constipation, and 9.1% of children with constipation had coexisting daytime urinary incontinence. In contrast, the same study showed that 3.9% of the children without constipation had daytime urinary incontinence. In one study, with successful treatment of constipation, the coexisting daytime incontinence was resolved in 89% of these patients, and recurrent urinary tract infections were avoided in all the affected children.[23] In addition, in neurologically normal children, treatment for urinary incontinence reduced the prevalence of functional fecal incontinence from 32% to 21%.[24]

Constipation is also a bothersome medical condition that affects 12% to 32% of middle-aged women.[3] Spence-Jones et al[25] first reported that constipation is an important factor in the pathogenesis of uterovaginal prolapse and stress urinary incontinence. Chronic constipation was considered the second strongest predictor for postpartum incontinence because of deteriorated support of the pelvic wall. Females who had undergone laparoscopic/vaginal hysterectomies or surgery for pelvic organ prolapse, or for urinary incontinence, had nearly a 2-fold higher risk for obstructive defecation.[26] Additionally, aging is also an important factor that affects constipation and LUTS. Charach et al[27] reported that treatment for constipation significantly improved LUTS and the patient's mood, sexual activity, and quality of life.

The mutual interaction between constipation and LUTS seems to be extensive and appears to be related to age. In pediatric patients, for example, daytime incontinence, enuresis, and recurrent urinary tract infections may be associated with chronic constipation that should not be overlooked by physicians. In middle-aged women, pelvic organ prolapse may result from the straining associated with chronic constipation. Management of chronic constipation for such conditions may benefit patients by alleviating LUTS and improving quality of life.[3,22] Further studies on the neuropathic population are necessary for understanding the vesical interaction between the rectum and bladder.

5. CKD and LUTS

The incidence of CKD is greater in Taiwan because of the increased prevalence of the leading causes of CKD, including hypertension, obesity, and diabetes.[28] The prevalence of CKD in Taiwan was 9.3% in 2003. CKD may be regarded as a clinical model of premature vascular aging. In the United States, fewer than 2% of CKD cases progress to end-stage renal disease (ESRD). Dialysis and renal replacement therapy are the therapeutic options for patients with ESRD.

Some researchers have reported that patients with chronic renal failure and those who had received kidney transplantation may develop LUTS. Wu et al reported that about one-fourth of patients with ESRD had moderate-to-severe LUTS as identified by the American Urological Association Symptom Index, regardless of the dialysis modality.[29] In the same study, they also determined that ESRD patients who receive peritoneal dialysis are more likely to present with nocturia and abdominal straining than those treated with hemodialysis. Zermann et al[30] reported that the major urodynamic findings in patients with ESRD are bladder oversensitivity, poor bladder compliance, detrusor overactivity, and detrusor sphincter dyssynergia. Oborn and Herthelius[31] reported that children and adolescents with chronic renal failure may suffer from LUTS, including incontinence (20%) and discontinuous flow (15%). They suspected that the high frequency of urinary tract infections in these patients may play a role in the development of LUTS.

The nature of LUTS after renal transplantation is another interesting issue for physicians. After successful transplantation, urine production is restored, and the lower urinary tract should adapt to urination again. However, this back-to-normal process might cause voiding dysfunction. Van der Weide et al[32] reported that frequent micturition, both during the day and at night, occurred in patients who had received renal transplantation. After renal transplantation, almost 50% of patients complained of high urinary frequency and 62% reported nocturia. Over a 3-year follow-up period, high urinary frequency and nocturia persisted among renal transplant recepients.[33] Mitsui et al[34] reported that the majority of cases of frequent urination may result from the polyuria and voiding dysfunction observed in renal transplant recipients. The influence of bladder dysfunction should be carefully observed in pediatric recipients, because 18.6% of pediatric transplant patients presented with a dysfunctional lower urinary tract.[35] In the future, more prospective studies that compare the change in bladder function and LUTS before and after renal transplantation may supply us with valuable information to better understand the association between CKD and LUTS.

6. Autoimmune diseases and LUTS

Autoimmune diseases result from an aberrant immune response in which an organism fails to recognize its constituent parts and initiates an immune response against its own tissue. There are several notable autoimmune diseases in humans, including systemic lupus erythematosus (SLE), Sjögren's syndrome, and rheumatoid arthritis. Autoimmune disease can directly affect the lower urinary tract function by attacking the central nervous system, upregulating the peripheral neurotransmission receptors, or depositing immune complexes in the bladder.

SLE is a systemic autoimmune disease that involves the production of antinuclear antibodies. These antibodies result in immune complexes attaching to major organs or connective tissue. SLE can cause interstitial cystitis-like syndrome, with a prevalence of approximately 1–2%. In severe cases, bilateral vesicoureteral stenoses causing hydronephrosis are present. The development of lupus cystitis may be associated with lupus enteritis.[36] These conditions may share similar abdominal and urinary symptoms, and both may respond to treatment with steroids or cyclophosphamide. An increase in serum anti-dsDNA levels has been reported to be one of the causes of severe lupus cystitis.[37] In epidemiological studies, researchers reported that patients with SLE may present with a variety of urinary symptoms, including high urinary frequency, urgency, weak stream, and incomplete emptying.[38,39] The increase in disease activity and central nervous system involvement in cases of SLE may be associated with the presence of LUTS. Urodynamic studies of SLE patients with LUTS may show a low cystometric bladder capacity that reveals the presence of a contracted bladder due to immune-complex deposition.

Sjögren's syndrome, which arises from an autoimmune process affecting the lacrimal and salivary glands, presents with dryness of the eyes and mouth in affected patients. It may occur either alone or within the context of another autoimmune disease, such as rheumatoid arthritis or SLE. Patients with primary and secondary Sjögren's syndrome may have autoantibodies that attack the M_3 muscarinic receptor in the bladder.[40] Walker et al[41] reported that patients with primary Sjögren's syndrome may suffer from more severe urinary urgency than those with osteoarthritis. In an animal study, passive transfer of Sjögren's syndrome IgG of humans into mice antagonized the M_3 muscarinic receptor and produced a compensatory increase in M3 muscarinic receptor expression in mice bladder.[40] This mechanism is considered to be the cause of OAB syndrome observed in humans with Sjögren's syndrome. In addition, patients with rheumatoid arthritis with secondary Sjögren's syndrome may show an increased risk of LUTS, especially urination frequency, in comparison with normal individuals.[42]

7. Metabolic syndrome and OAB

Metabolic syndrome consists of the risk factors for cardiovascular disease, including diabetes, insulin resistance, central obesity, dyslipidemia, and hypertension. The core elements of metabolic syndrome are reportedly diabetes, prediabetes, insulin resistance, and central obesity. Recent studies have provided significant support for a relationship between the presence of metabolic syndrome and OAB.

In an epidemiological study, Rohrmann et al[43] reported that men showing components of metabolic syndrome had an increased risk of nocturia, incomplete bladder emptying, weak stream, and hesitancy. Yu et al[44] also indicated that hyperlipidemia is associated with OAB in Taiwanese women. Furthermore, obesity alone or combined with diabetes can precipitate lower urinary tract dysfunctions such as OAB and stress urinary incontinence in females.[45] These findings demonstrate that the major presentations of metabolic syndrome can be associated with OAB. The core characteristics of metabolic syndrome, including diabetes, insulin resistance, and obesity, have been proposed to affect LUTS through the nitric oxide synthase/NO system, autonomic hyperactivity, Rho-kinase activation, and pelvic atherosclerosis.[46]

Animal studies suggest a link between the characteristics of metabolic syndrome and OAB. In an animal model of metabolic syndrome induced by fructose feeding, Tong and Cheng[47] reported that upregulation of M2,3 muscarinic receptors in the bladder was associated with the presentation of DO. The metabolic perturbations induced by long-term fructose feeding also contributed to DO and OAB symptoms, including proinflammation, increased oxidative stress, mitochondrial dysfunction, high levels of apoptosis in the detrusor muscle, and detrusor hypertrophy.[48,49] In progressive hypertension and hyperlipidemia in a spontaneously hypertensive and hyperlipidemic rat model, Nobe et al[50] also showed decreased rho kinase and protein kinase activities, both of which weaken the contractility of the detrusor.

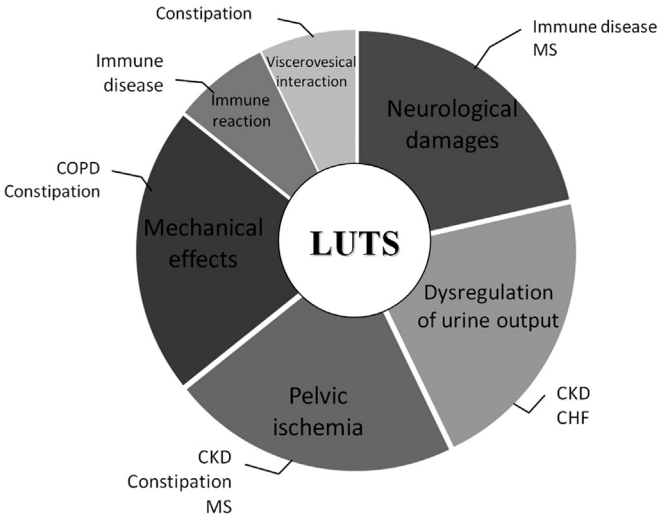

Fig. 1. How do medical diseases affect lower urinary tract function? CHF = chronic heart failure; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; MS = metabolic syndrome.

Hyperlipidemia may be the most important risk factor for OAB in cases of metabolic syndrome. Research conducted on a chronic hyperlipidemic rabbit model revealed that heritable hyperlipidemia can cause reduced bladder capacity, DO, and nerve degeneration of the bladder.[51] This observation could explain the aggravation of OAB symptoms along with hyperlipidemia observed in the human study.[44]

Oxidative stress may be induced by overexercise of the detrusor in the course of repeated DO and frequent urination.[49] In the early stages of bladder hyperactivity, the mitochondrial apparatus can supply the required high energy consumption. In the long run, however, the excessive energy demand and stimulation could exhaust the mitochondrial respiratory chain and impair its energy transduction system. Under such circumstances, oxidatively strained mitochondria become deformed and turn into a source of reactive oxidative stress, which initiates a self-destructing process in the mitochondrial respiratory apparatus, leading to protein damage, detrusor dysfunction, and, ultimately, atrophy.

In sum, through similar causative mechanisms, animal models mimicking metabolic syndrome may be predisposed to OAB and bladder dysfunction.

8. Conclusion

In this review of the literature, we have demonstrated that diseases have a strong impact on the presentation of LUTS. We illustrate the influence of various diseases in Fig. 1. CHF and the use of diuretics may result in OAB syndrome. The prevalence of OAB symptoms in CHF patients is associated with the severity of the CHF present. COPD may cause urgent incontinence in males, but stress urinary incontinence in females occurs because of the weakening of the pelvic floor. Constipation is associated with the urinary incontinence and recurrent UTIs in children. Treating the constipation would be beneficial for the improvement of urgent incontinence in children. The influence of autoimmune diseases and metabolic syndrome on the lower urinary tract function is comprehensive. Neurogenic insults, vasculopathy, and myopathy in autoimmune disease and metabolic syndrome may contribute to lower urinary tract dysfunction. Although a definite treatment for LUTS-related diseases has not been identified, clinicians should not neglect the impact of various diseases on LUTS. Further studies are needed to clarify the relationship between lower urinary tract dysfunction and major diseases.

Conflicts of interest statement

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

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